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08/776,350

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER	
UNGAR, S	
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DATE MAILED: 06/24/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

Responsive to communication(s) filed on Amendment Filed January 28, 1997

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 (month(s)) ~~or thirty days~~, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

Claim(s) 20 - 42 is/are pending in the application.
Of the above, claim(s) 23 + 35 is/are withdrawn from consideration.
Claim(s) _____ is/are allowed.
Claim(s) 20 - 22, 24-34 & 36-42 is/are rejected.
Claim(s) _____ is/are objected to.
Claim(s) _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
The drawing(s) filed on _____ is/are objected to by the Examiner.
The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
The specification is objected to by the Examiner.
The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of Reference Cited, PTO-892
Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
Interview Summary, PTO-413, 2 Sheets
Notice of Draftperson's Patent Drawing Review, PTO-948
Notice of Informal Patent Application, PTO-152

1. Claims 20-42 are pending and claims 23 and 35 have been withdrawn from further consideration by the examiner, under 37 CFR 1.142(b) as being drawn to a non-elected invention. Claims 20-22, 24-34 and 36-42 are currently under prosecution.

2. Restriction to election of a single disclosed species is required under 35 U.S.C. § 121:

Claims 20 and 30 are generic to a plurality of disclosed patentably distinct species comprising a method of treating a cancer wherein the cancer (a) is a tumor of the brain (claims 22, 32, 33) and (b) is a melanoma (claims 23 and 35).

3. Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

4. A telephone call was made to Arthur Crawford on June 5, 1997 to request an oral election to the above restriction requirement, a provisional election was made with traverse to prosecute the invention of species (a) tumors of the brain. Affirmation of this election must be made by applicant in responding to this Office action.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an

inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

7. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

Specification

8. The disclosure is objected to because of the following informalities:

(a) The specification should contain a separate section labeled "Brief Description of the Drawings". Appropriate correction is required.

(b) The attempt to **incorporate essential materials** into this application by reference to published patent application WO92/13943 disclosed on page 4 of the specification is improper because essential materials can only be incorporated by reference to (1) a U.S. patent or (2) an allowed U.S. application

meeting the conditions set forth in MPEP 608.01(p) section B. See In re Fouche 169 USPQ 429:439 F.2d 1237 (CCPA 1971).

Abstract

This application does not contain an Abstract of the Disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Applicant is reminded of the proper content of an Abstract of the Disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains.

If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure.

If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement.

In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof.

If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following: (1) if a machine or apparatus, its organization and operation; (2) if an article, its method of making; (3) if a chemical compound, its identity and use; (4) if a mixture, its ingredients; (5) if a process, the steps. Extensive mechanical and design details of apparatus should not be given.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

10. The specification is objected to under 35 USC 112, first paragraph, and Claims 20-22, 24-34 and 36-40 and 42 are rejected under 35 USC 112 first paragraph as failing to provide sufficient guidance to enable one skilled in the art to use a method of treating a cancer in a mammal which comprises administering an effective amount of a mutant herpes simplex virus type 1 which has a non-functional gamma 34.5 gene in the long repeat region.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. The specification and the claims contemplate the use of the HSV-1 mutant for the treatment of cancer in humans *in vivo*. The asserted utility of the claimed invention appears to be

based solely on in vitro and animal model data. The specification gives no guidance on or exemplification of a method for treating a cancer in a mammal, which reads on humans, which comprises administering an effective amount of a mutant herpes simplex virus type 1 which has a non-functional gamma 34.5 gene in the long repeat region. The specification gives guidance on and exemplification of only administration of the virus directly into a tumor in mouse brain. The claims as written are drawn to a wide range of methods of administration which may involve different routes, dosages, schedules, etc., and also exposes the virus to complex environments including blood cells and proteins, and also diverse organs such as the liver, lungs, kidney, and spleen, the fate and activity of the virus is unpredictable regarding its ability to reach or selectively infect tumor cells in humans *in vivo*. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure whether the instant method can be used with all methods of administration in humans because animal models do not fully mimic the biology of human patients.

11. The specification is further objected to under 35 USC 112, first paragraph, and Claims 20-22, 24-34 and 36-42 are rejected under 35 USC 112 first paragraph as failing to provide sufficient guidance to enable one skilled in the art to use a method of treating a cancer in a mammal which comprises administering an effective amount of a mutant herpes simplex virus type 1 which has a non-functional gamma 34.5 gene in the long repeat region.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention commensurate in scope with the claims. The claims as written are drawn to a HSV-1 virus which has a non-function gamma 34.5 gene. The gene can be inactivated by a variety of genetic manipulations which include deletions and/or insertions of nucleic acid residues that destroy the function of the gene. Yet, the specification only teaches the HSV-1 strain 17 deletion mutant HSV-1716 which has a 759 base pair deletion. The specification does not teach the inactivation of the gamma 34.5 gene with either insertions, or smaller or larger deletions and the specification fails to teach how to accurately predict the phenotype of the virus when, for example, neighboring genes are affected. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure whether any mutant HSV-1 with a non-functional gamma 34.5 gene will exhibit the functional properties of a mutant HSV-1 that will have attenuated neurovirulence and replicate in rapidly dividing tumor cells, but not in non dividing cells as opposed to a mutant HSV-1 that will replicate in all cells whether dividing or not, thus damaging rather than treating the mammal. Therefore, undue experimentation would be required to enable the claims.

12. The specification is further objected to under 35 USC 112, first paragraph, and Claims 25-29 and 36-39 are rejected under 35 USC 112 first paragraph as failing to provide sufficient guidance to enable one skilled in the art to use a method of treating a cancer wherein the mutant strain 17 virus has been modified within the Bam H1 s restriction fragment of the R_L terminal repeat.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention commensurate in scope with the claims. The claims as written read on all possible "modifications" of the Bam H1 s restriction fragment of the R_L terminal repeat and the language of the claims encompasses a variety of genetic manipulations (i.e deletions and/or insertions wherein these could include a single nucleotide deletion, a multiple nucleotide deletion and/or a combination of both as well as a variety of insertions and/or lesions. The specification fails to teach how to accurately predict the phenotype of a "modified" virus. For example, the specification does not indicate that a single nucleotide deletion within Bam H1 s could confer the phenotype of interest, nor does it indicate exactly where within Bam H1 such a single nucleotide alteration should be made. With regard to multiple nucleotide deletions, the specification also fails to accurately predict the phenotype of the virus when neighboring genes are affected. At the time of the filing it was known that the terminal portion of R_L encompasses multiple open reading frames. Broadly interpreted, the claims include deletions that are potentially larger than the 1716 species isolate deletion and claims 26, 27, 37 and 38 recite deletions that are larger than the 1716 deletion with neither guidance nor exemplification in the specification as to the functionality of the viruses claimed. Such deletions could result in a phenotype completely different from the desired one. Without specific disclosure as to the size and exact location of the deletions, one of skill in the art would not know where to make the deletions with the expectation of producing a virus with the phenotype of interest. Further, the specification fails to teach what mutations or amino acid substitutions/insertions are capable of attenuating the virus. The problem of predicting protein structure from sequence data and in turn utilizing

predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions (see Bowie et al (Science, 247:1306-1310, 1990, p. 1306, col.2). Therefore, in view of the speculative nature of the invention, the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

13. Claims 25-29 and 36-39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25-29 and 36-39 are vague and indefinite because claims 25 and 36 recite the term "modified". It is not clear how the virus is modified, for example, are nucleic acids inserted, deleted, or mutated?

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the

> art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

15. Claims 20, 22, 24-30, 32-34 and 36-41 are rejected under 35 U.S.C. § 103 as being unpatentable over Market et al (Neurosurgery, 32597-603, IDS item) in view of WO 92/13943 (IDS item).

The claims are drawn to a method of treating a cancer in a mammal or (2) a secondary metastatic tumor in the central nervous system of a mammal, comprising (1) administering to said mammal an effective amount of a mutant HSV-1 wherein the mutant virus is a mutant strain 17 virus which has a non-functional gamma 34.5 gene in the long repeat region, (2) wherein the cancer is a brain tumor, (3) wherein the cancer is a metastatic tumor, (4) wherein the mutant strain 17 virus has been modified within the Bam H1 s fragment of the long repeat region by deletions ranging from 0.1 to 3 kb, (5) wherein the virus strain is 1716, (6) wherein the mutant virus is administered directly into the cancer.

Market et al teach a successful method of treating a brain tumor in a mammal (mouse) comprising administering to said mammal an effective amount of an avirulent mutant HSV-1 virus (see Abstract) which has a non-functional gamma-34.5 gene (p. 598, para 3), by intraneoplastic injections of virus (p. 599, para 1) but do not disclose administering to a mammal an effective amount of a

mutant HSV-1 of species 1716 with a modified Bam H1 s fragment of the long repeat region with deletions ranging from 0.1 to 3 kb, administration to a metastatic tumor.

WO 92/13943 (IDS item) teaches the production of an avirulent deletion mutant HSV-1, species 1716, with a 759 bp deletion in the BAM H1 s restriction fragment of the long repeat region which has a nonfunctional gamma 34.5 gene.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the mutant HSV-1 of WO 92/13943 into the method of Market et al for the treatment of cancer in a mammal because Market et al teach a method of successfully treating a brain tumor in a mammal comprising administering to said mammal an effective amount of a mutant HSV-1 which has a non-functional gamma-34.5 gene and is therefore avirulent and because WO 92/13943 teaches an avirulent HSV-1 mutant. One of ordinary skill in the art would have expected to successfully treat cancer in a mammal by intraneoplastic injection of the HSV-1 mutant of 92/13943 because Market et al specifically teach that avirulent mutant HSV-1 virus with nonfunctional gamma 34.5 gene effectively reduces tumor size in mouse. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made and one of ordinary skill in the art would have been motivated to use the method of Market et al with a substituted HSV-1 mutant of WO 92/13943 on a secondary metastatic tumor because metastatic tumor cells have essentially similar characteristics of the primary cancer cells and it would be expected that injection of the virus directly into the

metastatic tumor would produce the same cancer killing effects seen in the primary tumor. Finally, the claimed HSV-1 mutant appears to be the same or an obvious variation of the known HSV-1 mutant absent a showing of unobvious differences.

16. No claims allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached at (703) 308-2731. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
June 18, 1997

LILA FEISEE
SUPERVISORY PATENT EXAMINER
GROUP 1800